PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a randomized controlled trial comparing warfarin with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis: The Danish Warfarin-Dialysis (DANWARD) trial
AUTHORS	Ballegaard, Ellen Linnea; Lindhard, Kristine; Lindhardt, Morten; Peters, Christian; Thomsen Nielsen, Finn; Tietze, Ida; Borg, Rikke; Boesby, Lene; Bertelsen, Marianne; Brøsen, Julie Maria; Cibulskyte-Ninkovic, Donata; Rantanen, Jesper; Mose, Frank; Kampmann, Jan; Nielsen, Alice; Breinholt, Johanne; Kofod, Dea; Bressendorff, Iain; Clausen, Peter; Lange, Theis; Køber, Lars; Kamper, Anne-Lise; Bang, Casper Niels; Torp-Pedersen, Christian; Hansen, Ditte; Grove, Erik; Gislason, Gunnar; Dam Jensen, Jens; Olesen, Jonas; Hornum, Mads; Rix, Marianne; Schou, Morten; Carlson, Nicholas

VERSION 1 – REVIEW

REVIEWER	Suh, Jung-Won Seoul National University Bundang Hospital, Department of Internal Medicine
REVIEW RETURNED	01-Dec-2023

GENERAL COMMENTS	This study is the first to explore whether vitamin K antagonists are safer and more effective than no oral anticoagulation in atrial fibrillation patients on chronic dialysis. The results could provide important guidance for doctors and directly influence clinical guidelines. There are some minor points to discuss. 1. In the exclusion criteria (2. Other indications for oral anticoagulation treatment), "prior atrial fibrillation" is included, and it looks confusing. 2. Severely anemic patients should be excluded from this trial. 3. Heparin use (vs. nafamostat mesylate) should be adjusted to assess bleeding events.

REVIEWER	Zwar, Nicholas Bond University, Health Sciences & Medicine
REVIEW RETURNED	02-Dec-2023

GENERAL COMMENTS	This is the protocol for a major RCT on a topic of importance and interest - whether treating patients with atrial fibrillation on chronic dialysis with warfarin reduces stroke and produces overall benefit. The description of the study is of high quality and the methods area appropriate with clearly defined population, intervention, comparator and outcomes.

	A few comments for the authors to consider - justification/reasons for an open label study design. The need to monitor INR is the likely reason, and makes sense, but should be discussed. - presumably patients on NOACs were excluded but I could not see this mentioned in the protocol

REVIEWER	Mitchell, Anneka University of Bath, Pharmacy and Pharmacology
REVIEW RETURNED	20-Dec-2023

GENERAL COMMENTS	This is a well written protocol describing a much needed study to inform clinical practice. I only have two minor queries: It would be useful if the authors could clarify why they included both new users of anticoagulation and existing users, there is likely to be some risk of healthy user/survivor bias despite the randomisation. Page 25 (66 of 84 in pdf) - states patients will be required to discontinue antiplatelets if allocated to warfarin group, however page 6 of 20 (pdf 8 of 84) states 'No specific recommendation regarding other medication. Including antiplatelets agents, is given in the protocol' – please clarify which is true

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Jung-Won Suh, Seoul National University Bundang Hospital
Comments to the Author:
This study is the first to explore whether vitamin K antagonists are safer and more effective than no oral anticoagulation in atrial fibrillation patients on chronic dialysis. The results could provide important guidance for doctors and directly influence clinical guidelines. There are some minor points to discuss.

1. In the exclusion criteria (2. Other indications for oral anticoagulation treatment), "prior atrial fibrillation" is included, and it looks confusing.

Our response:
The trial originally intended for sole inclusion of incident patients alone with subsequent amendment to include both incident and prevalent patients. The annotation of prior atrial fibrillation listed in the exclusion criteria is a mistype and has been corrected accordingly. Table 1 of the Main Document presents the correct inclusion- and exclusion criteria in accordance with current regulatory approvals. Of note, the protocol permitting inclusion of both prevalent and incident patients with atrial fibrillation was approved by both the Danish Medicines Agency as of June 24, 2021, and by the Regional Research Ethics Committee as of August 31, 2021.

2. Severely anemic patients should be excluded from this trial.

Our response:
This is a fair suggestion. Current trial participation entails exclusion of patients with ongoing or recent gastrointestinal bleeding, varices, substantial ulcerations, nondescript active bleeding, and/or cerebral hemorrhage. However, as noted there is no definite criterion for a minimum hemoglobin level. Although we appreciate the potential for inclusion of patients with critical anemia, our assessment – and experience so far – is that the combined effects of related exclusion criteria preclude inclusion of patients with severe anemia.

3. Heparin use (vs. nafamostat mesylate) should be adjusted to assess bleeding events.

Our response:
In line with the pragmatic nature of the study, warfarin prescription is non-protocolized and implemented in accordance with common clinical practice. In Denmark, the use of anticoagulation for prevention of dialysis filter clotting is almost exclusively limited to unfractionated and low-molecular weight (or related) heparins. Nafamostat mesylate is not currently available or used. Although we recognize the potential for greater bleeding risk due to dialysis-related anticoagulation, the risk is – in our contention – inherent and unavoidable for all patients on hemodialysis. We do however plan to compare bleeding rates between patients on hemo- and peritoneal dialysis. The issue is elaborated on in the methods section.

Methods, p. 6:
Randomization

In accordance with a computer-generated allocation, participants are randomized 1:1 to either treatment with warfarin or no treatment via a secure web application. Allocation is stratified by center using permuted blocks of random sizes, with block size and allocation ratio concealed. Participants not receiving anticoagulation at inclusion are randomized to either initiation of oral anticoagulation or to continued non-treatment. Participants treated with anticoagulation at inclusion are randomized to either continued anticoagulation with warfarin or discontinuation of treatment.

The date of randomization defines treatment initiation and beginning of follow-up. All study participants are treated in accordance with the randomization for at least 12 months. Participants included early in the trial remain under allocated treatment throughout the study until one year after inclusion of the last participant. In accordance with the pragmatic nature of the trial, ~~N~~no specific recommendation regarding other medications, including dialysis-related anticoagulation and antiplatelet agents, is given in the protocol. Except from INR measurements, patients in both allocation groups are monitored equally.

Reviewer: 2
Prof. Nicholas Zwar, Bond University
Comments to the Author:
This is the protocol for a major RCT on a topic of importance and interest - whether treating patients with atrial fibrillation on chronic dialysis with warfarin reduces stroke and produces overall benefit.

The description of the study is of high quality and the methods area appropriate with clearly defined population, intervention, comparator and outcomes.

A few comments for the authors to consider

- justification/reasons for an open label study design. The need to monitor INR is the likely reason, and makes sense, but should be discussed.

Our response:
We have made a few adjustments to the Strengths and limitations-bullets as presented below.

Strengths and limitations of this study, p. 3:

Strengths and limitations of this study

- A national, multicenter, investigator-initiated, open-label randomized clinical trial congruent with general clinical practice~~with adequate power to investigate treatment effect on clinical outcomes~~
- Adequate power to investigate harm and benefit of warfarin treatment on risk of bleeding, thromboembolic outcomes, and death
- Pragmatic study design permitting broad inclusion of patients on chronic dialysis with both incident and prevalent atrial fibrillation
- ~~First trial to investigate the efficacy and safety of vitamin K-antagonists compared with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis (hemo- and peritoneal dialysis)~~
- ~~Intervention is congruent with general clinical practice~~
- Open-label design enabling non-protocolized INR-dependent dose adjustments and continuous evaluation of requirements for dialysis-related anticoagulation and antiplatelet treatment
- Trial limited to allocation of warfarin vs. no treatment due to non-approval of direct-acting oral anticoagulants in chronic dialysis by the European Medicines Agency

- presumably patients on NOACs were excluded but I could not see this mentioned in the protocol

Our response:
This is a relevant consideration. As the European Medicines Agency has not approved the use of DOACs in patients on chronic dialysis*, treatment is considered off-label in Denmark. We have added a bullet on the topic to the Strengths and limitations-bullets as presented above.

*European Medicines Agency. Eliquis Product Information [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf
European Medicines Agency. Xarelto Product Information [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf
European Medicines Agency. Pradaxa Product Information. Available from: https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf
European Medicines Agency. Lixiana Product Information. Available from: https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf

Reviewer: 3
Mrs. Anneka Mitchell, University of Bath
Comments to the Author:
This is a well written protocol describing a much needed study to inform clinical practice. I

only have two minor queries:

It would be useful if the authors could clarify why they included both new users of anticoagulation and existing users, there is likely to be some risk of healthy user/survivor bias despite the randomisation.

Our response:
Previous trials of anticoagulation (VKA vs. DOAC) in patients with atrial fibrillation on chronic dialysis have demonstrated difficulties in including enough patients to make definite conclusions on treatment effects. This includes the RENAL-AF trial (n=154) and AXADIA-AFNET8 trial (n=97) despite inclusion of both prevalent and incident patients. For these reasons – and in the light of the pragmatic nature of this trial – we decided to include patients with both incident and prevalent atrial fibrillation, with or without ongoing anticoagulation, to hopefully gain enough power to make conclusions on treatment effects. Doing so, we agree that there is some risk of survivor bias, however, we have planned a number of sensitivity analyses to address this issue.

Page 25 (66 of 84 in pdf) - states patients will be required to discontinue antiplatelets if allocated to warfarin group, however page 6 of 20 (pdf 8 of 84) states 'No specific recommendation regarding other medication. Including antiplatelets agents, is given in the protocol' – please clarify which is true

Our response:
Thank you for considering the protocol in detail. We agree that the sentence on page 25 of the protocol (section titled "Initiation and maintenance of warfarin treatment") could be phrased clearer. The wording is "Patients allocated to oral anticoagulation will be required to discontinue antiplatelet drugs (i.e. aspirin or Adenosine diphosphate receptor inhibitors) unless specifically contraindicated." Hence, both statements are true: choice of concomitant antiplatelet therapy should be based on clinical evaluation of the specific patient. We have added details on the subject in the manuscript.

Methods, p. 6:
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The date of randomization defines treatment initiation and beginning of follow-up. All study participants are treated in accordance with the randomization for at least 12 months. Participants included early in the trial remain under allocated treatment throughout the study until one year after inclusion of the last participant. In accordance with the pragmatic nature of the trial, ~~N~~no specific recommendation regarding other medications, including dialysis-related anticoagulation and antiplatelet treatment, is ~~given~~ provided in the protocol. Except from INR measurements, patients in both allocation groups are monitored equally.
Strengths and limitations of this study, p. 3:

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VERSION 2 – REVIEW

REVIEWER	Suh, Jung-Won Seoul National University Bundang Hospital, Department of Internal Medicine
REVIEW RETURNED	11-Feb-2024

GENERAL COMMENTS	No further comments.

REVIEWER	Zwar, Nicholas Bond University, Health Sciences & Medicine
REVIEW RETURNED	04-Feb-2024

GENERAL COMMENTS	Authors have responded comprehensively to reviewer suggestions.

VERSION 2 – AUTHOR RESPONSE